

## Macrophage-specific expression of IL-37 in hyperlipidemic mice attenuates atherosclerosis

McCurdy S., Baumer Y., Toulmin E., Lee B., Boisvert W.

Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

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### Abstract

Copyright © 2017 by The American Association of Immunologists, Inc. inflammation, as well as the formation of lipid-laden macrophage foam cells within the vessel wall. IL-37 is recognized as an important anti-inflammatory cytokine expressed especially by immune cells. This study was undertaken to elucidate the role of macrophage-expressed IL-37 in reducing the production and effects of proinflammatory cytokines, preventing foam cell formation, and reducing the development of atherosclerosis. Expression of human IL-37 was achieved with a macrophage-specific overexpression system, using the CD68 promoter in mouse primary bone marrow-derived macrophages via retroviral transduction. Macrophage IL-37 expression in vitro resulted in decreased mRNA (e.g., IL-1B, IL-6, and IL-12) and secreted protein production (e.g., IL-6, M-CSF, and ICAM-1) of key inflammatory mediators. IL-37 expression also inhibited macrophage proliferation, apoptosis, and transmigration, as well as reduced lipid uptake, compared with controls in vitro. The in vivo effects of macrophage-expressed IL-37 were investigated through bone marrow transplantation of transduced hematopoietic stem cells into irradiated atherosclerosis-prone *Ldlr*<sup>2/2</sup> mice. After 10 wk on a high-fat/high-cholesterol diet, mice with IL-37-expressing macrophages showed reduced disease pathogenesis, which was demonstrated by significantly less arterial plaque development and systemic inflammation compared with control mice. The athero-protective effect of macrophage-expressed IL-37 has implications for development of future therapies to treat atherosclerosis, as well as other chronic inflammatory diseases.

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